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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/460,292	12/10/99	MANGELSDORF	D UTSD:596

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EXAMINER	
WOITACH, J	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/460,292	Applicant(s) MANGELSDORF ET AL.	
	Examiner Joseph Woitach	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-14,23-27,29,44 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-14,23-27,29,44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application is an original application filed December 10, 1999, which claims benefit to provisional application 60/111,894, filed December 10, 1998.

Applicants amendment filed May 11, 2001 has been received. The amendment to the specification reflecting a change in the inventorship has not been entered. The basis for not entering the amendment are discussed below. Claims 3, 15-20, 22, 28, 30-43 and 46-58 have been canceled. Claims 1, 2, 4-14, 21, 24-27, 44 and 45 have been amended. Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are pending and currently under examination.

Inventorship-Declaration filed under 37 CFR 1.48(a)

37 CFR 1.48 for correction of inventorship in a patent application, other than a reissue application states:

> (a) If the inventive entity is set forth in error in an executed § 1.63 oath or declaration in an application, other than a reissue application, and such error arose without any deceptive intention on the part of the person named as an inventor in error or on the part of the person who through error was not named as an inventor, the application may be amended to name only the actual inventor or inventors. When the application is involved in an interference, the amendment must comply with the requirements of this section and must be accompanied by a motion under § 1.634. Such amendment must be accompanied by:
>
> (1) A petition including a statement from each person being added as an inventor and from each person being deleted as an inventor that the error in inventorship occurred without deceptive intention on his or her part (emphasis added);
>
> (2) An oath or declaration by the actual inventor or inventors as required by § 1.63 or as permitted by § § 1.42, 1.43 or 1.47;
>
> (3) The fee set forth in § 1.17(i); and
>
> (4) If an assignment has been executed by any of the original named inventors, the written consent of the assignee (see § 3.73(b)).

In the instant case, the declaration filed May 11, 2001, paper number 13, is signed only by; David J. Mangelsdorf, Stephen D. Turley and John M. Dietschy. The declaration is not signed by the inventors who are to be added, Daniel J. Peet and Jean-Marc A. Lobaccaro, nor the inventor to be removed, Joyce J. Repa, as required by 37 CFR 148(a). In addition, the fee required as set forth in 1.17(i) was not authorized. Finally, the record indicates that the instant application is assigned to Board of Regents at The University of Texas System. As required by 37 CFR 1.48(a), the consent of the assignee must be obtained. See MPEP 201.

Declaration filed under 37 CFR 1.132

The Declaration of David Mangelsdorf under 37 CFR 1.132 filed June 6, 2001, paper number 14, is insufficient to overcome the rejection of claims 1-9, 14, 21-29, 44 and 45 based upon the 35 USC 102(a) rejection as anticipated by Peet *et al.* as set forth in the last Office action because: The declaration under 37 CFR 1.48(a) was not properly filed (see above). The proposed change to the named inventors of the instant application has not been entered. Therefore, the inventors of the present specification and the authors of the Peet *et al.* reference represent a different inventive entity.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a disruption of the endogenous nuclear oxysterol receptor gene (LXRα), wherein said disruption in said mouse results in the decrease of the LXRα protein and said mouse exhibits the inability to respond normally to dietary cholesterol does not reasonably provide enablement for transgenic mouse which comprises at least on endogenous LXRα allele that lacks the capacity to respond to dietary cholesterol. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants summarize the basis of the enablement rejection as being overly broad in three aspects: (a) claims should be limited to transgenic mice; (b) claims should be limited to mice having decreased LXRα protein; and claims should be limited to mice that cannot respond to dietary cholesterol. Applicants traverse the rejection but, in the interest of advancing prosecution, the claims have been amended to recite points (a) and (c). With regard to point (b), Applicants argue that various mutations can be introduced into a gene which would result in the expression of an inactive protein but not less total protein. See applicants amendment, pages 7-8. Applicants amendment has been fully considered but, not found persuasive.

It is noted that the claims have been amended to recite that the transgenic mouse comprising a LXRα which lacks the capacity to respond to dietary cholesterol. Examiner agrees with Applicant that various mutations or alterations of the LXRα allele which result in a nonfunctional LXRα polypeptide wherein said animal lacks the capacity to respond to dietary cholesterol would be obvious over the specific example disclosed as a working example in the instant specification. However, the claims as presently amended encompass more than mutations or alterations in the endogenous LXRα allele. As indicated in the previous office action (and below) in the 112, second paragraph, rejection, the claims encompass introducing a second heterologous polynucleotide which contains a LXRα allele sequence which renders the transgenic mouse incapable of responding to dietary cholesterol. Though it is conceivable that a dominant negative form of the LXRα polypeptide exists, the present specification does not teach such a coding sequence. Further, if such a polypeptide would exist, there is no guidance on what transgene expression levels would be necessary to achieve levels of the mutant LXRα polypeptide which would inactivate the endogenous LXRα polypeptide rendering the transgenic mouse incapable of responding to dietary cholesterol. As pointed out in the previous office action, Peet *et al.* teach that LXR receptors form heterodiameric complexes with RXR to form active complexes for the regulation of gene expression through the activation by both retinoids and oxysterols (page 693; bridging paragraph). Further, both Evans and Beato *et al.* conclude that 'recent developments shows that the controls of gene expression by steroid hormones is far more complex than was apparent at the time when the genes for SHRs were isolated. With more and

more players getting on stage, we realize not only this complexity but also the persuasive role steroid hormones play in a vast number of physiological and pathological precesses' (Beato pages 855-6; bridging paragraph). Manglelsdorf *et al.* described the nuclear superfamily as over 150 different proteins with a complex array of extracellular signals and transcriptional responses (page 841; first paragraph). While the review means to stress the commonalities among various signaling pathways and that 'it is possible to consider each receptor or each hormone in isolation and to extract common themes, body physiology is rarely so simple' (page 847; bottom of column 2) and concludes that while 'the advances of the last 10 years can be viewed with satisfaction, there is still a long and challenging journey ahead' (page 484; final line). Essentially, at the time of filing of the present application, LXRs represented a growing number of superfamily members with increasingly more complex function, particularly when extended to *in vivo* physiology. The present application has defined a novel function for the LXRα *in vivo* using transgenic mice with a disrupted allele, however, the specification of the present application, nor the art of record, has resolved the many complexities of the role of this receptor in all animals, nor has it resolved the role of this molecule for use in full the scope recited in the claims. Since the applicants have not disclosed all the nucleic acids encompassed by the claims, there is no way to predict efficiency nor expression of a transgene. Without an actual reduction to practice, it is possible to predict that introduction of a transgene or an alteration to a gene would result a predictable phenotype or even in a viable animal.

Method claims using the claimed non-human transgenic animal are included in this rejection because without clear guidance on how to make or use the transgenic animals encompassed by the claims, one of skill in the art would not know how to practice the claimed methods. In particular, due to the unpredictability of transgene behavior and resulting animal phenotype, one of skill in the art would not know what cholesterol-related or bile acid-related phenotypes to monitor. Further, due to the unpredictability of transgene behavior, it is not clear that any transgenic mouse other that one having a disrupted LXRα allele resulting in a null mutation or a nun-functional LXRα polypeptide would have a phenotype which could be used to study the effects on cholesterol or bile acid related metabolism.

Thus, in view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would have required undue experimentation by one of skill to practice the invention as claimed, and therefore, the rejection is maintained.

Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

In the interest of advancing prosecution, Applicants have amended the claims to encompass a transgenic mouse which cannot respond to dietary cholesterol. In addition,

Applicants argue that there is no written description issue for mice that contain mutations which merely alter, truncate or delete LXRα, but do not decrease its level of expression. See Applicants amendment, page 8.

Examiner agrees with Applicants arguments. The specification provides adequate written description for a transgenic mouse whose genome comprises a disruption of the endogenous nuclear oxysterol receptor gene (LXRα), wherein said disruption in said mouse results in the decrease of the LXRα protein and said mouse exhibits the inability to respond normally to dietary cholesterol.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 1, 2, 21, 26, 27, 44 and 45 are unclear in the recitation of 'comprises one endogenous LXRα allele that lacks the capacity to respond to dietary cholesterol' because the LXRα allele does not respond to cholesterol. It is the presence or absence of LXRα polypeptide which in concert with other retinoid receptors activates genes in response to dietary cholesterol levels. Amending the claim to more clearly define the relationship of the LXRα allele and

cholesterol metabolism would obviate the basis of the rejection. Further, it is unclear if an additional heterologous LXRα allele is added as a transgene, how this would reduce the capacity of the endogenous LXRα allele to respond to dietary cholesterol. It is the disruption of the endogenous LXRα allele resulting in a non-functional LXRα polypeptide which results in the inability to respond to dietary cholesterol. Dependent claims 4-14, 23-25 and 29 are include in this rejection because they fail to clarify the basis of the rejection.

Claims 4 and 5 are unclear in the recitation of 'contains an interruption in the LXRα coding sequence' because the endogenous LXRα allele contains introns and thus, the coding sequence of any transgenic mouse would contain an endogenous LXRα allele with a interrupted coding sequence.

Claims 6-9 are vague and unclear because not all mutations which generate a truncated LXRα polypeptide would result in a non-functional LXRα polypeptide, and meet the limitations set forth in claim 1. Amending the claims to more clearly indicate that the truncation results in an inactive LXRα polypeptide would obviate the basis of the rejection.

Claims 10 and 11 are vague and unclear in the recitation of 'contains a mutation in the regulatory region' because there is no functional language which defines the effect of the mutation. For example, the regulatory region could contain a base pair change which does not result in any effect in gene expression, or alternatively, increase gene expression of the LXRα and make the animal more responsive to dietary cholesterol.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 4-9, 14, 21, 23-27, 29, 44 and 45 stand rejected under 35 U.S.C. 102(a) as being clearly anticipated by Peet *et al.* (Cell 93:693-704; C45 in IDS).

Applicants point out that due to the amendment to the inventorship under 37 CFR 1.48(a), the only difference between the inventorship of the instant specification and the authorship of the Peet *et al.* paper is the inclusion of Ma, Janowksi and Hammer as coauthors. Applicants argue that in light of the Declaration of Dr. Mangelsdorf explaining that Ma, Janowksi and Hammer did not contribute to the conception of the subject matter included in Peet *et al.* paper and instantly claimed, the Peet et al. paper is not 'by another' and does not qualify as prior art under 102(a). See Applicants amendment, pages 9-10. Applicants arguments have been fully considered but not found persuasive.

As indicated above, the inventorship of the instant application has not been changed and Joyce J. Repa is still an inventor. Further, the Declaration of Dr. Mangelsdorf lists Daniel J. Peet and Jean-Marc A. Lobaccaro as contributing to the inventive concept of the invention instantly claimed. Thus, because the inventorship of the instant application and the authors of the Peet *et al.* are different, the teachings in Peet *et al.* still represent the teachings by another. It is noted by

Examiner that if the change of inventorship as requested in applicants amendment is affected, the Declaration of Dr. Mangelsdorf would be found persuasive.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Claims 10-13 appear to be free of the prior art of record because the prior art of record fails to teach or suggest the disruption of the promoter region of the LXRα gene with an inducible/repressible promoter. However, these claims are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608. The fax number for group 1600 is (703)308-4724.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pickney whose telephone number is (703) 305-3553.

Joseph T. Woitach

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1630